Remarks

Amendments to the Specification

Applicants have noticed that several inconsistencies appear in paragraph 47 of the specification (starting at line 20 on page 10) as compared with the contents of the Figures, the Description of the Drawing (paragraphs 18-24, p. 6, lines 6-27), and the Description of the Sequence Listing (paragraphs 27-32 at p. 7, lines 1-13). The amendments indicated above are to correct paragraph 47 so that it accurately reflects the contents of the Figures, the Description of the Drawing, the Description of the Sequence Listing, and the contents of the sequence listing. In particular, SEQ ID NO: 5 is the sequence of the lysostaphin protein encoded by the lysostaphin gene identified by Heinrich, as indicated at p. 6, lines 19-21 and presented in Figure 15B. As is immediately evident, Figure 15A presents the nucleic acid sequence of the corresponding gene, which is presented as SEQ ID NO: 9 in the Sequence Listing. SEQ ID NO: 6 is in fact the sequence of the wild type lysostaphin *protein* encoded by the lysostaphin gene identified by Thumm and Gotz, as indicated at p. 7, lines 12-13, while the corresponding gene is presented in Fig. 16 (rather than Fig. 14), as indicated at p. 6, lines 22-25, and in SEQ ID NO: 10. Since the corrections simply correct typographical errors in order to conform paragraph 47 to the Figures, the Description of the Drawing, the Description of the Sequence Listing, no new matter is added by the amendment.

Applicants have also noticed that the Sequence Listing contains some errors, i.e., the listed organism and/or description of the sequence are incorrect or incomplete for six of the sequences. Applicants are in the process of preparing a Substitute Sequence Listing to correct these errors. The sequences themselves, in particular SEQ ID NO: 3, are correct. However, the Sequence Listing should have indicated that SEQ ID NO: 3 is an altered gene from *S. simulans.*

Rejections under 35 U.S.C. §112

Claims 1-3 and 27-44 stand rejected as failing to comply with the written description requirement. The Examiner states that the specification and claims do not indicate what common attributes or characteristics are shared by members of the genus and thus have not described a function which is shared by the modified gene which would adequately describe the

genus (office action of 7/27/04, p. 4, lines 15-19). Applicants respectfully submit that the amended claims meet the written description requirement for each of the following reasons.

Firstly, claims 1 and 35 as amended now contain two specific functions that are shared by proteins encoded by the modified genes, in accordance with the Examiner's indication during a telephonic interview on November 3, 2004, that recitation of such function(s) would be helpful in addressing the alleged deficiency in written description. Accordingly, claims 1 and 35 have been amended to recite that the protein kills *Staphylococcus aureus* cells by hydrolyzing pentapeptide links of the *Staphylococcal* cell wall. Support for these functions is found at p. 10, lines 7-9, which describes the activity of active lysostaphin as follows: "Lysostaphin has endopeptidase activity and kills cells by hydrolyzing the pentapeptide links of staphylococcal cell walls, causing the cells to lyse...one requirement of the present invention is that the protein be expressed and secreted at sufficient concentrations *in vivo* to kill *S. aureus*." The enzymatic activity of lysostaphin is highly specific. For example, lysostaphin selectively hydrolyzes glycyl-glycine peptide bonds but does not hydrolyze glycylserine and serylglycine peptide bonds (Thumm and Gotz, *Mol. Microbiol.* 23(6), 1251-1265, 1997, incorporated by reference in the instant application at p. 7, line 13.)

The Written Description Guidelines indicate that describing a genus of nucleic acids by virtue of the ability of members of the genus to hybridize to a listed nucleic acid is permissible because such a limitation "yields structurally similar molecules" (USPTO Written Description Guidelines, p. 39). Similarly, the Written Description Guidelines recognize that a description of an antigen is sufficient to describe an antibody that binds to the antigen based on the functional characteristics of antigen-antibody interaction (USPTO Written Description Guidelines, p. 60). Applicants note that the structural features that distinguish one antibody from another, which presumably are of primary importance for describing the antibody, reside in the variable portions of the antibody, whose sequence is unknown and is defined purely on the basis of its ability to mediate interaction with the antigen. These examples demonstrate that a molecule may be adequately described by providing a description of a second molecule with which that molecule interacts. In the instant case, the claimed genes encode an active lysostaphin protein that interacts with a substrate that is specifically hydrolyzed by lysostaphin, i.e., the pentapeptide links of *S. aureus* cell walls.

Applicants therefore respectfully submit that the Examiner's statement that "Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The protein itself is required." is not a fully accurate reflection of current law. Providing a sequence is not the only way in which the written description requirement can be met, as indicated in the USPTO Written Description Guidelines and confirmed in *Enzo Biochem Inc. v. Gen-Probe, Inc., et al.*, 323 F.3d 956 (Fed. Cir. 2002). In that case, the court referred to the PTO Guidelines as stating that "functional claiming is permissible when the claimed material hybridizes to a disclosed substrate" (*Id.* at 966). As noted above, in the instant application, the claimed material encodes an active lysostaphin protein that specifically recognizes and hydrolyzes a disclosed substrate, i.e., glycyl-glycine peptide bonds in the *Staphylococcus aureus* cell wall, thereby describing a function which is shared by the modified genes and adequately describe the genus.

Secondly, Applicants submit that the specification either explicitly or implicitly discloses a sufficient number of species of modified genes to support a claim to a genus. In rejecting the instant claims the Examiner stated that "Applicants sole working example of SEQ ID NO:3 simply does not allow those of skill in the art to recognize a genus of claims based on this solitary example." Applicants respectfully submit that the application discloses a number of species in addition to SEQ ID NO: 3. Applicants specifically disclose that lysostaphin contains two sites for glycosylation in mammalian cells, each of which may be modified in accordance with the teachings of the instant invention. Applicants specifically disclose modifying these sites by substituting glutamine (Gln) for asparagine (Asn) within the Asn-X-(Ser/Thr) sequence(s) (p. 14, lines 17-24). Furthermore, Applicants describe additional preferred alterations that would disrupt glycosylation (p. 14, lines 25-26). For example, Applicants disclose that conservative substitutions are preferred since one of ordinary skill in the art will recognize that such substitutions are more likely to result in proteins that retain activity than are nonconservative substitutions (p. 14, lines 26 – p. 15, line 1). Applicants indicate that polar (hydrophilic) amino acids that may be conservatively substituted for one another include serine, threonine, cysteine, tyrosine, asparagine, and glutamine (p. 15, lines 3-4). Thus Applicants disclose an additional five preferred substitutions that can be made within the Asn-X-(Ser/Thr) sequences. Applicants submit that the specification therefore discloses a large set of sequences that is representative of the claimed genus.

Thirdly, Applicants note that the law has repeatedly recognized that, "It is not necessary that the application describe the claim limitations in greater detail than the invention warrants." *Martin v. Mayer*, 823 F.2d 500 (Fed. Cir. 1987) and furthermore, "The written description requirement does not require the applicant 'to describe exactly the subject matter claimed...'", *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000), provided that the inventor "conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims" *Id.* The standard is thus one of reasonableness and does not require the recitation of every sequence that would fall within the scope of the claims. The specification thoroughly describes Applicants' contribution to the art as embodied by the instant claims. In particular, the specification teaches the existence and location of mammalian glycosylation sites in naturally occurring lysostaphin. The specification further teaches that modification of the sequence of lysostaphin so as to disrupt glycosylation of the protein by mammalian cells allows secretion of active lysostaphin from such cells. One of ordinary skill in the art would recognize that these teachings clearly indicate Applicants' possession of the claimed genus notwithstanding the fact that sequences falling within the genus have not been exhaustively enumerated.

In summary, Applicants submit that claims 1 and 35 as amended now recite sufficient structural and functional limitations that one of ordinary skill in the art would recognize that Applicants were in possession of the claimed genus and that the specification provides a representative set of species that fall within the genus. Withdrawal of the rejection is respectfully requested.

Claims 1-3 and 27-44 also stand rejected on the ground that the limitation requiring that the claimed protein is recognized by a polyclonal antibody that recognizes the naturally occurring version of lysostaphin is not adequately supported by the specification. Applicants respectfully disagree. One of ordinary skill in the art would recognize that since the teachings of the Examples exemplify the invention, a general method of identifying a lysostaphin protein such as by virtue of its recognition by a polyclonal antibody, would be applicable to other lysostaphin proteins generated as described in the specification. However, in the interests of furthering prosecution, Applicants have removed reference to the polyclonal antibody from claims 1 and 35. Withdrawal of the rejection is respectfully requested.

New claims

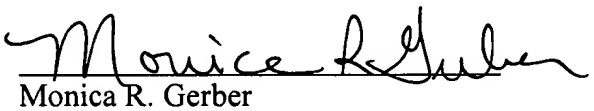
Applicants have added four new claims in accordance with the Examiner's suggestion that setting forth specific sequences would be helpful. New claim 45 recites an isolated nucleic acid that codes for an active lysostaphin protein encoded by a nucleic acid having a sequence set forth in SEQ ID NO: 3, wherein the active lysostaphin protein has both of its two sites for N-linked glycosylation in mammalian cells (Asn-X-(Ser/Thr)) altered with respect to the wild type lysostaphin protein, or a variant of SEQ ID NO: 3 that encodes an active lysostaphin protein in which only one of the sites for *N*-linked glycosylation is altered with respect to the wild type lysostaphin protein, wherein the active lysostaphin protein kills *Staphylococcus aureus* cells by hydrolyzing pentapeptide links of *Staphylococcus aureus* cell walls. New claim 46 recites that the Asn residue in either or both of the sites for *N*-linked glycosylation is deleted or replaced by a different amino acid. New claim 47 recites that the Asn residue in either or both of the sites for *N*-linked glycosylation is replaced by Gln. New claim 48 recites an isolated nucleic acid that comprises SEQ ID NO: 3 or a variant thereof in which only one of the two Asn codons in the sites for *N*-linked glycosylation is altered relative to the wild type sequence. Support for the new claims is found at p. 14, lines 17-24, describing Applicants' modification(s) to the sequence of naturally occurring lysostaphin (replacement of either or both of the two Asn codons in the *N*-linked glycosylation sites by Gln), and at p. 7, lines 6-7, indicating that SEQ ID NO: 3 (Fig. 13) is an inventive altered lysostaphin gene.

In conclusion, in view of the amendments and remarks presented herein, none of the cited art anticipates any of the claims pending in the instant application, and the application complies with the requirements of 35 U.S.C. §112. Applicants therefore respectfully submit that the present case is in condition for allowance. A Notice to that effect is respectfully requested.

If, at any time, it appears that a phone discussion would be helpful, the undersigned would greatly appreciate the opportunity to discuss such issues at the Examiner's convenience. The undersigned can be contacted at (617) 248-5000 or (617) 248-5071 (direct dial).

Please charge any fees associated with this filing, or apply any credits, to our Deposit Account No. 03-1721. In addition, in accordance with 37 C.F.R. 1.136(a)(3), please consider this statement as authorization to charge our Deposit Account to encompass any necessary Petitions for Extension of Time and fees associated therewith in the instant case.

Respectfully submitted,



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